

REMARKS

This Reply is being filed in response to the Office Action mailed from the U.S. Patent and Trademark Office on January 4, 2005, in which claims 1-53 were rejected under 35 U.S.C. §103(a). Further, claims 1-53 were rejected under obviousness-type double patenting. With this Reply, Applicants respectfully contend that the Office Action has not established a prima facie case of obviousness. As such, Applicants respectfully request withdrawal of the rejections under §103(a) and obviousness-type double patenting; further, Applicants respectfully request reconsideration and allowance of pending claims 1-53.

Claims rejected under 35 U.S.C. §103(a):

In order to establish a prima facie case of obviousness, the MPEP states:

To establish a prima facie case of obviousness, three basic criteria must be met. **First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.** The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)...MPEP §2142. (Emphasis added).

Applicants respectfully disagree with the Office Action's obviousness rejection of the claimed compound wherein the claimed compound comprises an azacrown, a calixarene, and an unsubstituted aryl group(s) wherein each has been carefully selected to optimize lithium detection. Lithium ions, sodium ions and potassium ions are extremely similar in structure and properties. As such, devising a compound that will exclusively bind to one of these ions is an unpredictable art. As demonstrated by FIG. 1 and FIG. 2 of the present application, the Applicants have devised such a compound. As will be discussed in detail below, the Applicants respectfully disagree that the claimed invention is an obvious modification of a compound that had been optimized for potassium detection (as disclosed by the cited art). As such, Applicants respectfully request reconsideration and allowance of pending claims 1-53.

The Applicants have claimed a compound which allows for the specific detection of lithium over potassium ions and sodium ions. The claimed compound is able to selectively detect lithium because a specific calixarene is engaged to a specific azacrown. Furthermore, a specific unsubstituted aryl group is engaged to the azacrown. In identifying a sensor and a compound capable of selectively detecting lithium, many questions need to be answered: for example, (1) what is the ideal size of an azacrown to bind lithium?; (2) which substituents, if any, should be located on the azacrown ring?; (3) should a calixarene be engaged to the azacrown?; (4) if so, what substituents should be on the azacrown ring?; (5) what compound should be engaged to the azacrown ring in order to deliver a measurable fluorescence?; and (6) how do all these groups react and interact with lithium as opposed to potassium and/or sodium? FIG. 1 and FIG. 2 of the present application illustrate the Applicants success in identifying such a compound that may specifically detect lithium. Applicants respectfully disagree that it would have been obvious to modify a potassium sensor in order to determine the correct answer to each of the several questions listed above. As such, Applicants respectfully request reconsideration and allowance of pending claims 1-53.

The Office Action cites: (1) the Benco et al. reference and the Kim et al. reference wherein each disclose a calixarene engaged to an azacrown wherein the azacrown is engaged to an unsubstituted aryl group for the specific purpose of detecting potassium ions and not detecting lithium ions; and (2) the Pacey et al. patent which discloses an azacrown engaging a substituted benzyl group for the detection of lithium ions. It is unclear from the Pacey et al reference, to be discussed below, if the ability to detect lithium ions over other ions (i.e., sodium or potassium ions) comes from: (1) the size of the azacrown; or (2) the use of solvents optimized to deter sodium and/or potassium ions. The Pacey et al. patent refers to each of these as having an effect on the desired selectivity. It is reasonable to expect that both led to the purported success of the compound disclosed by the Pacey et al. patent. However, the Applicants respectfully disagree that the Pacey et al. patent teaches one how to modify the compound of the Benco et al. reference and/or the Kim et al. reference in order to teach the compound of the pending application.

Benco et al. and Kim et al.

The Benco et al. reference discloses a compound capable of selectively binding potassium ions. More specifically, the Benco et al. reference discloses:

Our focus in this work and in earlier studies has been the construction of fluoroionophores specific for potassium and sodium cations in the human physiological range that can be incorporated into solid-state optical sensors for clinical diagnostic measurements. To this end, we have synthesized II (and its model compound I), which combines with the known optical response of anthryl azacrown-6 to potassium ions with expected enhanced selectivity provided by coupling the azacrown to a 1,3-alternate calix[4]arene. Described here are the results of these initial studies, potentially promising increased selectivity for the potassium over sodium and other alkali metal ions and good sensitivity for potassium ions in the human physiological range. (Benco et al., Page 34)(Emphasis added).

Regarding selectivity of the azacrown ring, the Benco et al. reference discloses:

Since it is our eventual intention to use molecules similar to II as a sensor for the detection of potassium ions in blood sample, the selectivity of II for potassium ions in blood samples, the selectivity of II for potassium over other analytes is an important consideration. Given the structural similarities between II and 1,3-alternate calix[4]arenes [1], it is reasonable to expect similar binding properties. Therefore, we expect the metal ion complexation in II is governed by electrostatic interactions, particularly with the azacrown oxygen atoms, and through cation- π interactions, but selectively is controlled primarily by a size fit effect and steric effects from the propyl substituents appended to the two rotated aryl rings of the calix[4]arene [1]...(the Benco et al. reference; Page 37)(Emphasis added).

As shown by the above-identified passages, the intention of the experiments disclosed in the Benco et al. reference was to devise a compound capable of detecting potassium and not detecting lithium ions. The Benco et al. reference discloses that they "expect the metal ion complexation in II is governed by electrostatic interactions, particularly with the azacrown oxygen atoms, and through cation- π interactions, but selectively is controlled **primarily by a size fit effect and steric effects from the propyl substituents appended to the two rotated aryl rings of the calix[4]arene [1].**" However, this expectation does not make obvious how one would: (1) modify the compound in order to exclusively bind lithium ions and not potassium ions or sodium ions; or (2) how one would modify the compound in order to exclusively bind

sodium ions to the exclusion of lithium ions and potassium ions. Further, the above-identified passage indicates that an interaction between the propyl substituent and the potassium ions play a significant role in the binding specificity of the compound of the Benco et al. reference. As such, the Applicants argue that this passage would not teach those skilled in the art how to modify the compound to obtain the experimental results displayed in FIG. 1 and FIG. 2 of the present application.

Similarly, the Kim et al. reference discloses a complex having a calixarene bound to an azacrown and capable of detecting various cations; however, like the Benco et al. reference, the Kim et al. reference discloses a compound which has been developed for binding potassium ions and/or silver ions. More specifically, the Kim et al. reference discloses a compound with multiple binding locations (i.e., one location may bind potassium ions, while a second location may bind silver ions). Nowhere in the Kim et al. reference is it disclosed, taught or suggested how one should modify the disclosed compound in order to exclusively bind lithium ions; more specifically, the Kim et al. reference does not disclose the specific size and/or substituents of an azacrown ring engaged to a calixarene which would allow for the exclusive binding and detection of lithium ions.

As such, neither the Benco et al. reference nor the Kim et al reference, alone or in any combination, disclose or suggest how one would modify their respective compounds in order to obtain a compound which selectively binds lithium ions to the exclusion of potassium ions and/or sodium ions. Furthermore, as argued in Applicants' Reply of November 18, 2004, modifying the compound of the Benco et al. reference or the compound of the Kim et al. reference to bind lithium ions would produce a compound that would "change the principle of operation of the primary reference [and] render the reference inoperable for its intended purpose." (See MPEP §2143.01).

Pacey et al.

The Pacey et al. patent discloses a compound capable of detecting lithium; however, the Pacey et al. patent merely discloses an azacrown engaging a substituted benzyl group. The Pacey et al. patent does not teach or suggest an azacrown engaged to a calixarene; furthermore,

the Pacey et al. patent does not disclose an azacrown engaged to a calixarene and then engaged to a unsubstituted aryl fluorophore.

In discussing the selectivity of the disclosed compound, the Pacey et al. patent discloses:

A basic buffer is required in the reagent system to ensure optimum properties. Both NaOH and KOH are suitable buffers, but potassium hydroxide is generally preferred due to interference effects of the sodium ion on the absorbance during spectrophotometric analysis. The optimum concentration of hydroxide buffer is approximately 1×10^{-2} M to 1×10^{-1} M, although lower concentrations can be employed with some sacrifice in sensitivity. (the Pacey et al. patent; Col. 2, Lines 60-68)(Emphasis added).

As such, the Pacey et al. patent credited the lithium selectivity of the disclosed compound to the structure of the compound and to the use of a specific buffer (i.e., a buffer used to interfere with sodium ions). Therefore, it is unclear after reading the Pacey et al. patent to what extent the increased lithium selectivity may be attributed to: (1) the size of the azacrown; (2) the use of a basic buffer; or (3) the use of a substituted benzyl group engaged to the azacrown. Furthermore, the crown of the Pacey et al. patent comprises three oxygen atoms wherein the aza-crown engaged to a calixarene (as in the present invention) contains two oxygen atoms--this is bound to have an effect on lithium binding sensitivity and/or selectivity.

As such, neither the Benco et al. reference, the Kim et al reference nor the Pacey et al. patent, alone or in any combination, disclose, teach or suggest an azacrown engaged to a calixarene and having an unsubstituted aryl group engaged to the azacrown wherein the compound specifically binds to lithium ions. Many factors need to be taken into account in such an unpredictable process as developing a compound suitable for lithium detection. Questions such as: (1) how will the size of the aza-crown affect the binding selectivity; (2) how will the various substituents on the aza-crown ring affect the binding selectivity; (3) how will the choice of a fluorophore affect selectivity. The experimental results shown in FIGS. 1 and 2 show that the Applicant has successfully answered these questions and has developed a novel compound suitable for lithium detection.

Barnard et al.

The Barnard et al. patent was cited by the January 4, 2005 Office Action because the reference discloses a fluoroionophore engaged to a solid support and acting as a sensor. However, the Barnard et al. patent does not cure the deficiency of the Benco et al. reference, the Kim et al reference, nor the Pacey et al. patent. More specifically, the Barnard et al. patent does not disclose or suggest a compound having an azacrown engaged to a calixarene and having a fluorophore engaged to the azacrown wherein the compound specifically binds to lithium ions. As such, neither the Barnard et al. patent, the Benco et al. reference, the Kim et al. reference, nor the Pacey et al. patent, alone or in any combination disclose, teach or suggest the Applicants' claimed invention.

Claims Rejected Under Obviousness-Type Double Patenting:

The Office Action rejected claims 1-53 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 6,660,526 to Benco et al. ("the '526 patent") in view of the Benco, Pacey and Barnard references. The August 18, 2004 Office Action stated:

The patented claims are directed to a molecule, device and method that encompass the molecule, device and method taught by Benco above, therefore they differ from the instant claims as the Benco reference differs from the instant claims. **Thus for the reasons given above, the instant claims are obvious in view of the patented claims.** (August 18, 2004 Office Action, Page 5)(Emphasis added).

As noted by the Office Action, the Benco reference (discussed above) discloses the same subject matter as the '526 patent--that is, both disclose a calixarene which selectively binds to potassium ions and does NOT bind to lithium ions. More specifically, the compound of the '526 patent is different (larger azacrown) than the compound of the present invention. The compound of the present invention would render the object of the '526 patent (a potassium sensor) inoperable. As such, Applicants respectfully requests withdrawal of the rejection under the judicially created doctrine of obviousness-type double patenting and allowance of pending claims 1-53.

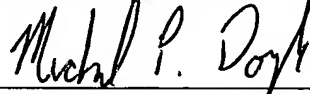
With this Amendment, Applicants have made an earnest effort to respond to all issues raised in the Office Action of January 4, 2005, and to place all claims presented in condition for

allowance. No amendment made was for the purpose of narrowing the scope of any claim, unless Applicants have argued herein that such amendment was made to distinguish over a particular reference or combination of references.

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

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